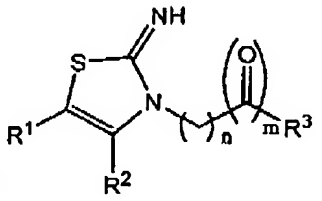
AMENDMENTS TO THE CLAIMS

This listing of claims replaces all prior versions, and listings, of claims in the application.

1. (Original) A method of inhibiting cell death in a mammal, wherein the method comprises administering to a mammal an effective amount of a composition comprising a cell protection factor covalently linked to a bone targeting agent via a linkage that is cleaved under physiological conditions, whereby the cell protection factor is released from the bone targeting agent *in vivo* to inhibit cell death.

2. (Original) The method of claim 1, wherein the cell protection factor is a temporary p53 inhibitor.

3. (Withdrawn) The method of claim 2, wherein the cell protection factor is a compound of Formula I:



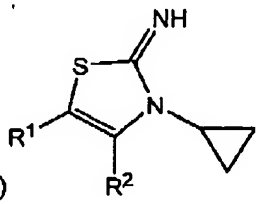
(I)

wherein m is 0 or 1, n is an integer from 1 to 4,

R^1 and R^2 are taken together to form an aliphatic or aromatic carbocyclic 5- to 8-membered ring, optionally substituted with one or more straight or branched C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, fluoro, chloro, bromo, nitro, amino, C_1-C_6 alkylamino, and/or C_4-C_{14} aromatic or heteroaromatic moieties, and

R^3 is selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, and a phenyl group, wherein the alkyl group, the alkoxy group, or the phenyl group is optionally substituted with one or more straight or branched C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, fluoro, chloro, bromo, nitro, amino, C_1-C_6 alkylamino, and/or C_4-C_{14} aromatic or heteroaromatic moieties, and optionally forms a C_3-C_6 cycloalkyl when R^3 is connected to the carbon alpha to the thiazole ring.

4. (Withdrawn) The method of claim 3, wherein m is 0, n is 2, and R^3 is a one-carbon alkyl such that the three-carbon chain forms a cyclopropyl group, whereby the cell protection factor is a compound of Formula X:

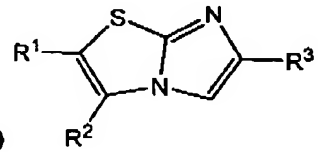


(X)

wherein R^1 and R^2 are taken together to form an aliphatic or aromatic carbocyclic 5- to 8-membered ring optionally substituted with one or more straight or branched C_1-C_6 alkyl, C_1-C_6 alkoxy, fluoro, chloro, bromo, nitro, amino, C_1-C_6 alkylamino, and/or C_4-C_{14} aromatic or heteroaromatic moieties.

5. (Withdrawn) The method of claim 3, wherein R^1 and R^2 are taken together to form a 5- or 6-membered aliphatic carbocyclic ring optionally substituted with one or more C_1-C_6 alkyl groups.

6. (Original) The method of claim 2, wherein the cell protection factor is a compound of Formula IV:



(IV)

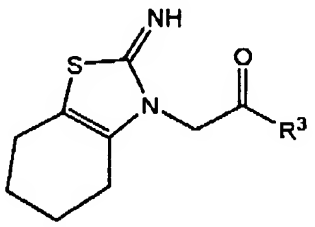
wherein R^1 and R^2 are taken together to form an aliphatic or aromatic carbocyclic 5- to 8-membered ring, optionally substituted with one or more straight or branched C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, fluoro, chloro, bromo, nitro, amino, C_1-C_6 alkylamino, and/or C_4-C_{14} aromatic or heteroaromatic moieties, and

R^3 is selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, and a phenyl group, wherein the alkyl group, the alkoxy group, or the phenyl group is optionally substituted with one or more straight or branched C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, fluoro,

chloro, bromo, nitro, amino, C_1-C_6 alkylamino, and/or C_4-C_{14} aromatic or heteroaromatic moieties.

7. (Original) The method of claim 6, wherein R^1 and R^2 are taken together to form a 5- or 6-membered aliphatic carbocyclic ring optionally substituted with one or more C_1-C_6 alkyl groups.

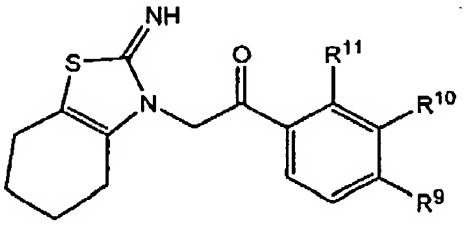
8. (Withdrawn) The method of claim 5, wherein the cell protection factor is a compound of Formula II:



(II)

wherein R^3 is selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, and a phenyl group, wherein the alkyl group, the alkoxy group, or the phenyl group is optionally substituted with one or more straight or branched C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, fluoro, chloro, bromo, nitro, amino, C_1-C_6 alkylamino, and/or C_4-C_{14} aromatic or heteroaromatic groups.

9. (Withdrawn) The method of claim 8, wherein the cell protection factor is a compound of Formula III:



(III)

wherein R^9, R^{10}, and R^{11} are each independently a hydro, methyl, fluoro, chloro, bromo, nitro, amino, methoxy, or phenyl moiety.

10. (Withdrawn) The method of claim 9, wherein the cell protection factor is 2-[2-imino-4,5,6,7-tetrahydro-1,3-benzothiazol-3(2H)-yl]-1-(4-methylphenyl)-1-ethanone or 2-[2-imino-4,5,6,7-tetrahydro-1,3-benzothiazol-3(2H)-yl]-1-(biphenyl)-1-ethanone.

11. (Original) The method of claim 1, wherein the inhibited cell death is bone marrow cell death.

12. (Original) The method of claim 11, wherein the cell death is caused by exposure to at least one chemical or radiation.

13. (Original) The method of claim 6, wherein the inhibited cell death is bone marrow cell death.

14. (Original) The method of claim 13, wherein the cell death is caused by exposure to at least one chemical or radiation.

15. (Withdrawn) The method of claim 9, wherein the inhibited cell death is bone marrow cell death.

16. (Withdrawn) The method of claim 15, wherein the cell death is caused by exposure to at least one chemical or radiation.

17. (Original) The method of claim 1, wherein the mammal comprises at least one tumor.

18. (Original) The method of claim 17, wherein the mammal comprises at least one $p53^{+}$ tumor.

19. (Original) The method of claim 6, wherein the mammal comprises at least one tumor.

20. (Original) The method of claim 19, wherein the mammal comprises at least one $p53^+$ tumor.

21. (Withdrawn) The method of claim 9, wherein the mammal comprises at least one tumor.

22. (Withdrawn) The method of claim 21, wherein the mammal comprises at least one $p53^+$ tumor.

23. (Original) The method of claim 1, wherein the bone targeting agent is selected from the group consisting of a bisphosphonate, a hydroxybisphosphonate, a phosphonate, a phosphate, an aminomethylenephosphonic acid, and an acidic peptide.

24. (Withdrawn) The method of claim 3, wherein the bone targeting agent is selected from the group consisting of a bisphosphonate, a hydroxybisphosphonate, a phosphonate, a phosphate, an aminomethylenephosphonic acid, and an acidic peptide.

25. (Original) The method of claim 6, wherein the bone targeting agent is selected from the group consisting of a bisphosphonate, a hydroxybisphosphonate, a phosphonate, a phosphate, an aminomethylenephosphonic acid, and an acidic peptide.

26. (Withdrawn) The method of claim 9, wherein the bone targeting agent is selected from the group consisting of a bisphosphonate, a hydroxybisphosphonate, a phosphonate, a phosphate, an aminomethylenephosphonic acid, and an acidic peptide.

27. (Original) The method of claim 1, wherein the linker is an acid-cleavable linker.

28. (Withdrawn) The method of claim 3, wherein the linker is an acid-cleavable linker.

29. (Original) The method of claim 6, wherein the linker is an acid-cleavable linker.

30. (Withdrawn) The method of claim 9, wherein the linker is an acid-cleavable linker.

31. (Original) The method of claim 27, wherein the linker is an enol ether, ketal, imine, oxime, hydrazone, semicarbazone, acylimide, or methylene radical.

32. (Withdrawn) The method of claim 28, wherein the linker is an enol ether, ketal, imine, oxime, hydrazone, semicarbazone, acylimide, or methylene radical.

33. (Original) The method of claim 29, wherein the linker is an enol ether, ketal, imine, oxime, hydrazone, semicarbazone, acylimide, or methylene radical.

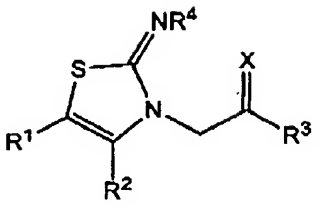
34. (Withdrawn) The method of claim 30, wherein the linker is an enol ether, ketal, imine, oxime, hydrazone, semicarbazone, acylimide, or methylene radical.

35. (Original) The method of claim 1, wherein the linker is a hydrolytically cleavable linker.

36. (Original) The method of claim 1, wherein the linker is cleaved enzymatically.

37. (Original) The method of claim 1, wherein the mammal is a human.

38. (Withdrawn) A compound of Formula V:



(V)

wherein R^1 and R^2 are taken together to form an aliphatic or aromatic carbocyclic 5- to 8-membered ring, optionally substituted with one or more straight or branched C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, fluoro, chloro, bromo, nitro, amino, C_1-C_6 alkylamino, and/or C_4-C_{14} aromatic or heteroaromatic moieties,

R^3 is selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, and a phenyl group, wherein the alkyl group, the alkoxy group, or the phenyl group is optionally substituted with one or more straight or branched C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, fluoro, chloro, bromo, nitro, amino, C_1-C_6 alkylamino, and/or C_4-C_{14} aromatic or heteroaromatic moieties,

R^4 is hydrogen or an C_1-C_6 acyl group when X is Q, or R^4 is Q when X is a carbonyl or protected carbonyl, and

X is Q, a carbonyl, or a protected carbonyl,

wherein Q is an organic moiety that contains a nucleophilic or electrophilic reacting group and is cleavable under physiological conditions, thereby releasing a temporary p53 inhibitor.

39. (Withdrawn) The compound of claim 38, wherein Q is an organic moiety that is cleavable under acidic physiological conditions.

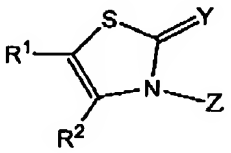
40. (Withdrawn) The compound of claim 38, wherein Q is an organic moiety that is hydrolytically cleavable under physiological conditions.

41. (Withdrawn) The compound of claim 38, wherein Q is an enol ether, ketal, imine, oxime, hydrazone, semicarbazone, acylimide, or methylene radical.

42. (Withdrawn) The compound of claim 38, wherein Q is an organic moiety that is enzymatically cleavable.

43. (Withdrawn) The compound of claim 38, wherein Q is A-J, wherein A is an organic moiety that is cleavable under physiological conditions, and J is a bone targeting agent.

44. (Withdrawn) A compound of Formula VI:

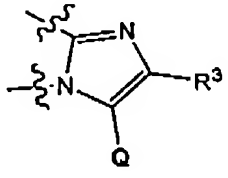


(VI)

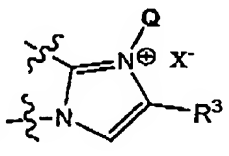
wherein R^1 and R^2 are taken together to form an aliphatic or aromatic carbocyclic 5- to 8-membered ring, optionally substituted with one or more straight or branched C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, fluoro, chloro, bromo, nitro, amino, C_1-C_6 alkylamino, and/or C_4-C_{14} aromatic or heteroaromatic moieties,

R^3 is selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, and a phenyl group, wherein the alkyl group, the alkoxy group, or the phenyl group is optionally substituted with one or more straight or branched C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, fluoro, chloro, bromo, nitro, amino, C_1-C_6 alkylamino, and/or C_4-C_{14} aromatic or heteroaromatic moieties, and

Y and Z taken together complete a 5-member imidazole ring of Formula VII or Formula VIII,



(VII)



(VIII)

wherein X^- is selected from the group consisting of a chloride, a bromide, a fluoride, an iodide, an acetate, a formate, a phosphate, a sulfate, and other pharmaceutically acceptable anions, and Q is an organic moiety that contains a nucleophilic or electrophilic reacting group and is cleavable under physiological conditions.

45. (Withdrawn) The compound of claim 44, wherein Q is an organic moiety that is cleavable under acidic physiological conditions.

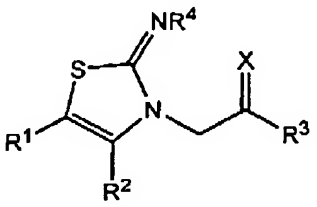
46. (Withdrawn) The compound of claim 44, wherein Q is an organic moiety that is hydrolytically cleavable under physiological conditions.

47. (Withdrawn) The compound of claim 44, wherein Q is an enol ether, ketal, imine, oxime, hydrazone, semicarbazone, acylimide, or methylene radical.

48. (Withdrawn) The compound of claim 44, wherein Q is an organic moiety that is enzymatically cleavable.

49. (Withdrawn) The compound of claim 44, wherein Q is A-J, wherein A is an organic moiety that is cleavable under physiological conditions, and J is a bone targeting agent.

50. (Withdrawn) A compound of Formula V:



(V)

wherein R^1 and R^2 are taken together to form an aliphatic or aromatic carbocyclic 5- to 8-membered ring, optionally substituted with one or more straight or branched C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, fluoro, chloro, bromo, nitro, amino, C_1-C_6 alkylamino, and/or C_4-C_{14} aromatic or heteroaromatic moieties,

R^3 is selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, and a phenyl group, wherein the alkyl group, the alkoxy group, or the phenyl group is optionally substituted with one or more straight or branched C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, fluoro, chloro, bromo, nitro, amino, C_1-C_6 alkylamino, and/or C_4-C_{14} aromatic or heteroaromatic moieties,

X is A-J, a carbonyl, or a protected carbonyl, and

R^4 is hydrogen or an C_1-C_6 acyl group when X is A-J or R^4 is A-J when X is a carbonyl or protected carbonyl,

wherein A is an organic moiety that is cleavable under physiological conditions, and J is a bone targeting agent.

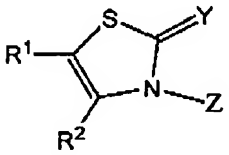
51. (Withdrawn) The compound of claim 50, wherein A is an organic moiety that is cleavable under acidic physiological conditions.

52. (Withdrawn) The compound of claim 50, wherein A is an organic moiety that is hydrolytically cleavable under physiological conditions.

53. (Withdrawn) The compound of claim 50, wherein A is an organic moiety that is enzymatically cleavable.

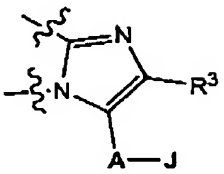
54. (Withdrawn) The compound of claim 50, wherein the bone targeting agent is selected from the group consisting of a bisphosphonate, a hydroxybisphosphonate, a phosphonate, a phosphate, an aminomethylenephosphonic acid, and an acidic peptide.

55. (Withdrawn) A compound of Formula VI:

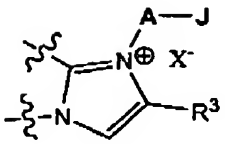


(VI)

wherein R^1 and R^2 are taken together to form an aliphatic or aromatic carbocyclic 5- to 8-membered ring, optionally substituted with one or more straight or branched C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, fluoro, chloro, bromo, nitro, amino, C_1-C_6 alkylamino, and/or C_4-C_{14} aromatic or heteroaromatic moieties, and Y and Z taken together complete a 5-member imidazole ring of Formula VII or Formula VIII,



(VII)



(VIII)

wherein R^3 is selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, and a phenyl group, wherein the alkyl group, the alkoxy group, or the phenyl group is optionally substituted with one or more straight or branched C_1-C_6 alkyls, C_1-C_6 alkoxy, hydroxy, fluoro, chloro, bromo, nitro, amino, C_1-C_6 alkylamino, and/or C_4-C_{14} aromatic or heteroaromatic moieties, X^- is selected from the group consisting of a chloride, a bromide, a fluoride, an iodide, an acetate, a formate, a phosphate, a sulfate, and other pharmaceutically acceptable anions, and A is an organic moiety that is cleavable under physiological conditions, and J is a bone targeting agent.

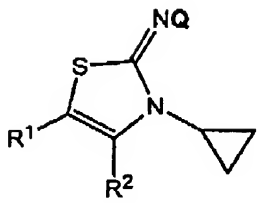
56. (Withdrawn) The compound of claim 55, wherein A is an organic moiety that is cleavable under acidic physiological conditions.

57. (Withdrawn) The compound of claim 55, wherein A is an organic moiety that is hydrolytically cleavable under physiological conditions.

58. (Withdrawn) The compound of claim 55, wherein A is an organic moiety that is enzymatically cleavable.

59. (Withdrawn) The compound of claim 55, wherein the bone targeting agent is selected from the group consisting of a bisphosphonate, a hydroxybisphosphonate, a phosphonate, a phosphate, an aminomethylenephosphonic acid, and an acidic peptide.

60. (Withdrawn) A compound of Formula IX:



(IX)

wherein R^1 and R^2 are taken together to form an aliphatic or aromatic carbocyclic 5- to 8-membered ring, optionally substituted with one or more straight or branched C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, fluoro, chloro, bromo, nitro, amino, C_1-C_6 alkylamino, and/or C_4-C_{14} aromatic or heteroaromatic moieties,

wherein Q is an organic moiety that contains a nucleophilic or electrophilic reacting group and is cleavable under physiological conditions.

61. (Withdrawn) The compound of claim 60, wherein Q is an organic moiety that is cleavable under acidic physiological conditions.

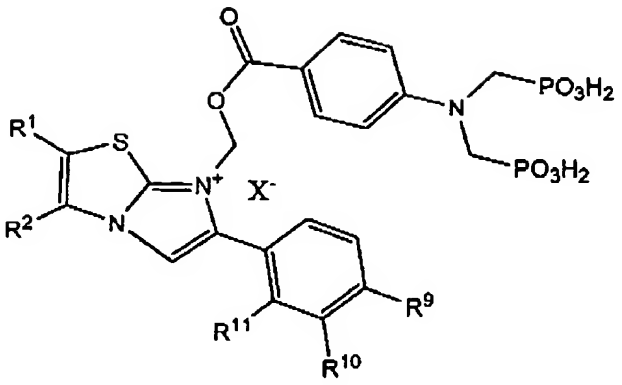
62. (Withdrawn) The compound of claim 60, wherein Q is an organic moiety that is hydrolytically cleavable under physiological conditions.

63. (Withdrawn) The compound of claim 60, wherein Q is an organic moiety that is enzymatically cleavable.

64. (Withdrawn) The compound of claim 60, wherein Q is A-J, wherein A is an organic moiety that is cleavable under physiological conditions and J is a bone targeting agent.

65. (Withdrawn) The compound of claim 44, wherein Q in Formula VIII is -CH_2O-.

66. (Withdrawn) The compound of claim 65, wherein the compound is Formula XI:

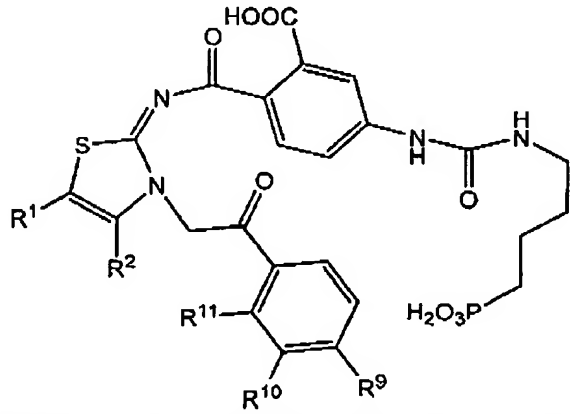


(XI)

wherein R^1 and R^2 are taken together to form an aliphatic or aromatic carbocyclic 5- to 8-membered ring, optionally substituted with one or more straight or branched C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, fluoro, chloro, bromo, nitro, amino, C_1-C_6 alkylamino, and/or C_4-C_{14} aromatic or heteroaromatic moieties, X^- is selected from the group consisting of a chloride, a bromide, a fluoride, an iodide, an acetate, a formate, a phosphate, a sulfate, and other pharmaceutically acceptable anions, and

R^9, R^{10}, and R^{11} are each independently a hydro, methyl, fluoro, chloro, bromo, nitro, amino, methoxy, or phenyl moiety.

67. (Withdrawn) The compound of claim 66, wherein the compound is Formula XII:



(XII)

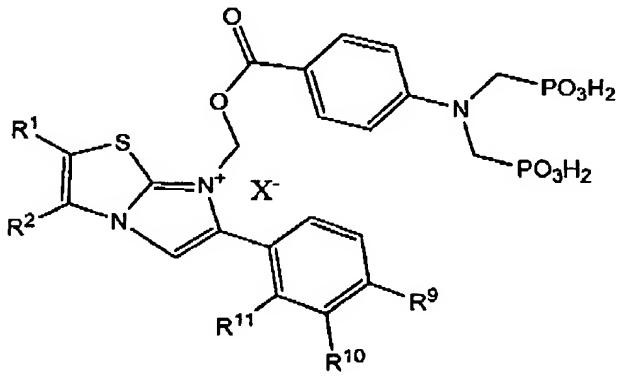
wherein R^1 and R^2 are taken together to form an aliphatic or aromatic carbocyclic 5- to 8-membered ring, optionally substituted with one or more straight or branched C_1-C_6 alkyl, C_1-C_6

alkoxy, hydroxy, fluoro, chloro, bromo, nitro, amino, C_1-C_6 alkylamino, and/or C_4-C_{14} aromatic or heteroaromatic moieties, and

R^9, R^{10}, and R^{11} are each independently a hydro, methyl, fluoro, chloro, bromo, nitro, amino, methoxy, or phenyl moiety.

68. (Withdrawn) The compound of claim 55, wherein A of Formula VIII is -CH_2O- and J is a bone targeting agent.

69. (Withdrawn) The compound of claim 68, wherein the compound is Formula XI:

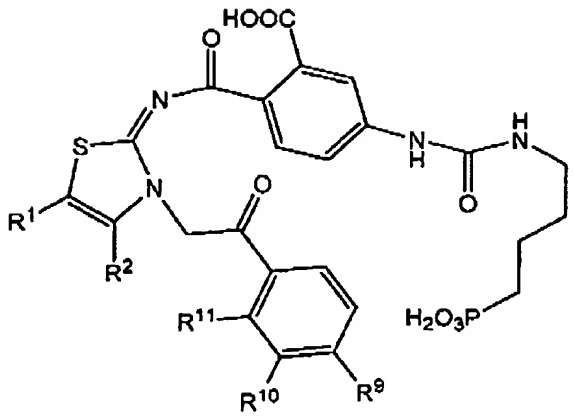


(XI)

wherein R^1 and R^2 are taken together to form an aliphatic or aromatic carbocyclic 5- to 8-membered ring, optionally substituted with one or more straight or branched C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, fluoro, chloro, bromo, nitro, amino, C_1-C_6 alkylamino, and/or C_4-C_{14} aromatic or heteroaromatic moieties, X^- is selected from the group consisting of a chloride, a bromide, a fluoride, an iodide, an acetate, a formate, a phosphate, a sulfate, and other pharmaceutically acceptable anions, and

R^9, R^{10}, and R^{11} are each independently a hydro, methyl, fluoro, chloro, bromo, nitro, amino, methoxy, or phenyl moiety.

70. (Withdrawn) The compound of claim 69, wherein the compound is Formula XII:



(XII)

wherein R^1 and R^2 are taken together to form an aliphatic or aromatic carbocyclic 5- to 8-membered ring, optionally substituted with one or more straight or branched C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, fluoro, chloro, bromo, nitro, amino, C_1-C_6 alkylamino, and/or C_4-C_{14} aromatic or heteroaromatic moieties, and

R^9, R^{10}, and R^{11} are each independently a hydro, methyl, fluoro, chloro, bromo, nitro, amino, methoxy, or phenyl moiety.

71. (Withdrawn) The compound of claim 38, wherein X is a carbonyl and R^4 is Q or A, wherein Q is an acid cleavable group, and wherein A selected from the group consisting of 4-aminophthalic acid, succinic acid, 4-aminophenylacetic acid, and 4-aminobenzoic acid.

72. (Withdrawn) The compound of claim 43, where the bone targeting agent is selected from a group consisting of alendronate, pamidronate, 4-aminobutylphosphonic acid, N,N,N,N-tetrakis-(phosphonomethyl)-ethylenediamine, 1-hydroxyethane-1,1-diphosphonic acid, phytic acid, N,N,N,N-tetrakis(methylphosphono)-1,5,8,12-tetraazacyclotetradecane, N,N-bis(methylphosphono)-4-amino-benzoic acid, nitrilotri(methylphosphonic acid), aspartyl hexapeptide, and glutamyl hexapeptide.

73. (Withdrawn) The compound of claim 50, where the bone targeting agent is selected from a group consisting of alendronate, pamidronate, 4-aminobutylphosphonic acid, N,N,N,N-tetrakis-(phosphonomethyl)-ethylenediamine, 1-hydroxyethane-1,1-diphosphonic acid, phytic acid, N,N,N,N-tetrakis(methylphosphono)-1,5,8,12-tetraazacyclotetradecane,

N,N-bis(methylphosphono)-4-amino-benzoic acid, nitrilotri(methylphosphonic acid), aspartyl hexapeptide, and glutamyl hexapeptide.

74. (Withdrawn) The compound of claim 55, where the bone targeting agent is selected from a group consisting of alendronate, pamidronate, 4-aminobutylphosphonic acid, N,N,N,N-tetrakis-(phosphonomethyl)-ethylenediamine, 1-hydroxyethane-1,1-diphosphonic acid, phytic acid, N,N,N,N-tetrakis(methylphosphono)-1,5,8,12-tetraazacyclotetradecane, N,N-bis(methylphosphono)-4-amino-benzoic acid, nitrilotri(methylphosphonic acid), aspartyl hexapeptide, and glutamyl hexapeptide.

75. (New) The method of claim 7, wherein the cell protection factor is pifithrin-β.